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## **Selective Breeding for Temperament and Vulnerability to Addiction: A Genetic, Genomic and Neural Characterization of Behavioral Undercontrol and Overcontrol.**

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To study hereditary influences on temperament, we selectively bred rats based on exploratory locomotion (EL) in a novel environment. The selectively bred High Responders (bHR) are highly active in a novel environment, in contrast to the selectively bred Low Responders (bLR) that are minimally active. These lines represent two extreme temperamental phenotypes that exemplify behavioral under-control (sensation-seeking, drug-seeking, impulsivity, aggression, addiction liability), and behavioral over-control (anxiety, depression, social inhibition). Typically, bHRs show greater vulnerability to addiction. However, bLRs are highly reactive to chronic stress which significantly enhances their responsiveness to drugs of abuse. Thus, our model captures two paths to drug abuse that exist in humans: Sensation-seeking and high reactivity to stress.

To identify DNA variants underlying these phenotypes, we created a bHRxbLR F0-F1-F2 cross and performed shallow whole-genome sequencing. We identified high heritability of several behaviors. We identified 10 significant and conditionally independent loci for six behavioral traits, mostly on Chromosome 1 (Chitre, Hebda-Bauer et al, 2023).

We also carried out RNAseq analyses on the F0 and F2 rats and uncovered robust differential expression patterns between the lines. Our top hits implicated differences in microglial, mitochondrial and synaptic functions. Several genes exhibited differential expression associated with EL in F2 rats, seven of which were located near (+/-1MB) QTLs related to EL and anxiety. We will provide examples of specific genes that appear especially likely to mediate the effects of selective breeding on temperament based on convergent evidence between our model and human genetic studies (Hebda-Bauer, Hagenauer et al, 2023).